The mitotic roles of Polo-like kinase

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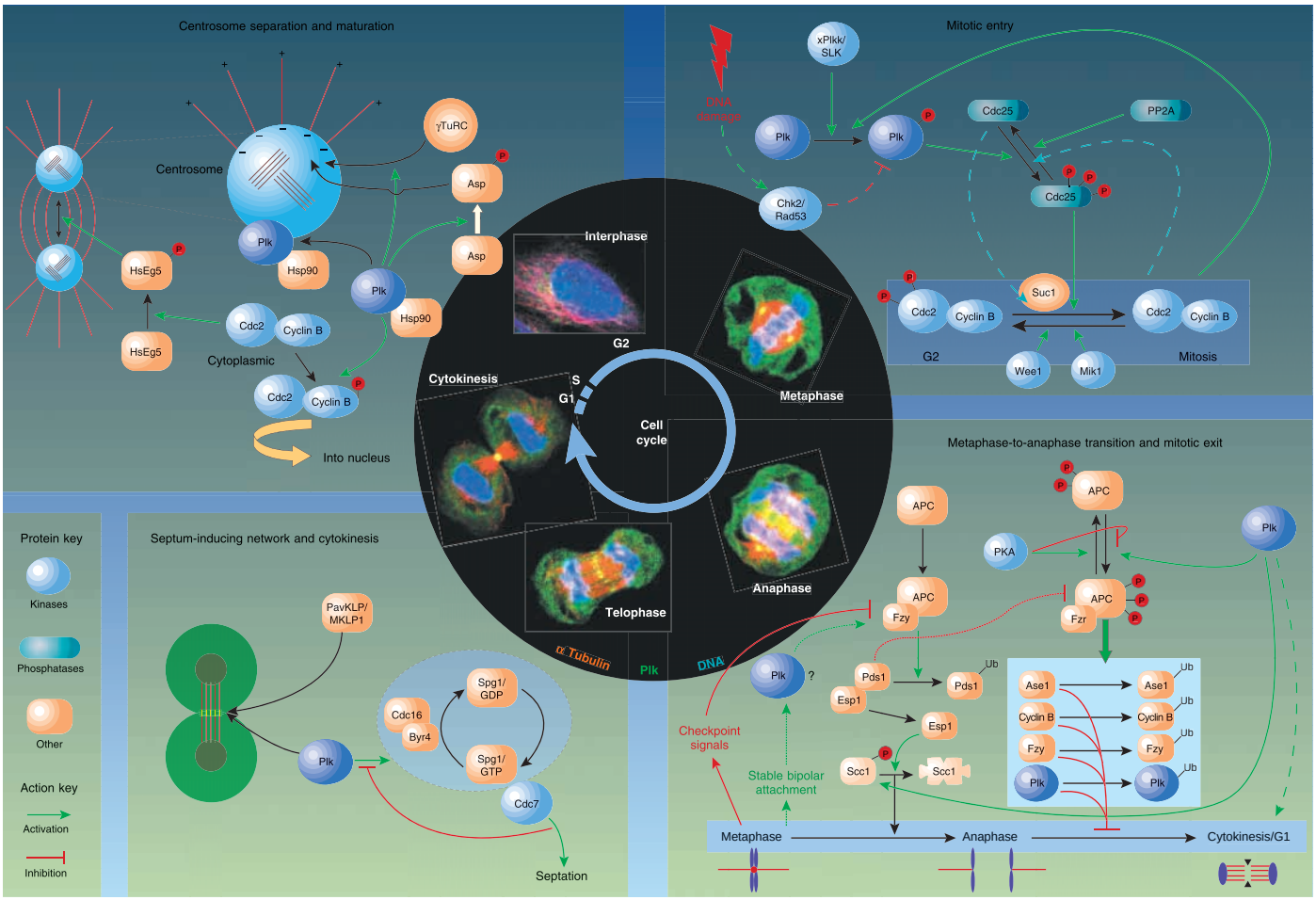
The Polo-like protein kinases (Plks) are a conserved family of enzymes that play a variety of roles in the passage of cells through M phase (for reviews see Glover et al., 1998; Nigg, 1998). Named after the *Drosophila polo* gene originally identified through a recessive maternal effect lethal mutation, conserved Plk homologues have been identified in yeast, *Xenopus*, *C. elegans* and mammals. The interactions presented here represent information drawn from all these systems and integrated to form an overall picture. As with any undertaking of this type, there will be slight inconsistencies between specific roles for Plks in different species.

Mitotic entry

At the entry to mitosis, Cdc25 has a basal phosphatase activity that can partially activate Cdc2 by removing the inhibitory phosphates added by Wee1 and Mik1. Cdc2 can then feed back and phosphorylate Cdc25, further activating it. This process is linear and involves an intermediary kinase in addition to Cdc2. The amplification of Cdc2 activity needed for mitotic entry does not occur until Plk becomes activated. Cdc25 is then further activated, which results in the burst of Cdc2 activation needed for mitotic entry. Plk can directly activate Cdc25 and thus probably plays a role in the positive feedback loop that operates during $p34^{cdc2}$ activation at the G2-M transition.

Centrosome separation and maturation

Plks have also been shown to have a role in centrosome maturation and separation. If Plk is mutated or inhibited, a mitotic bipolar spindle fails to form, and cells produce monopolar spindles. In human cells Plk appears to stimulate the centrosome's microtubule-nucleating activity upon mitotic entry. Furthermore, it seems to facilitate recruitment of γ-tubulin and activates Asp at the centrosome. Asp is a microtubule-associated protein that accumulates at the minus ends of the microtubules and helps focus the microtubule ends and maintain their proximity to the



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centrosome. Another microtubule-associated protein, the plus-end-directed motor HsEg5, is involved in separation of the centrosomes to opposite poles of the cell and the organisation of mitotic asters. HsEg5 is phosphorylated and activated by Cdc2–Cyclin B, which in turn is activated by Plk.

The metaphase-anaphase transition and mitotic exit

Plks can activate certain functions of the anaphase-promoting complex (APC), an E3 ubiquitin-protein ligase that directs the degradation of anaphase inhibitors such as Pds1p in budding yeast and Cut2p in fission yeast. By activating the APC, Plk also induces Ca^{2+}-triggered destruction of Cyclin B and inactivation of $p34^{cdc2}$ and, consequently, M-phase exit. Mouse Plk phosphorylates and activates the bacterially expressed APC components Cdc16 and Cdc27 in vitro, which suggests Plk may directly regulate the APC. The substrate specificity of the APC is regulated by its interactions with Fizzy (Fzy) and Fizzy-related (Fzr). When the APC is in a complex with Fzy, it directs the breakdown of components that inhibit sister chromatid separation, such as the securin Pds1. This leads to activation of the separin Esp1, which cleaves the cohesin Scc1. While in complex with Fzr, it directs the breakdown of inhibitors of mitotic exit such as Cyclin B and the spindle component Ase1.

The septum-inducing network and cytokinesis

Plks are required to promote the onset of cytokinesis. In the absence of fission yeast *plo1*, multinucleate cells are produced in which neither an actin ring nor a septum has been formed, and over-expression of yeast or human Plks leads to the formation of multiple septa at any stage of the cell cycle. This indicates the potential of the enzyme to overcome the dependence of this process upon the completion of mitosis. The septum-inducing network has a two-part GTPase-activating protein (GAP) and a GTP-binding protein, which signals septum formation through the kinase Cdc7. In *S. pombe*, the GAP comprises Cdc16 and Byr4 and the GTP-binding protein is Spg1. Plk regulates this pathway and, once activated, the pathway feeds back and inhibits Plk. In *Drosophila*, *polo* seems to reorganise the central region of the spindle in late M phase, co-localising with Pav-KLP, a microtubule motor protein of the kinesin family, at the spindle midzone and the midbody during cytokinesis. Pav-KLP has a role in establishing the structure of the telophase spindle and providing a framework for the assembly of the contractile ring. Similarly, in *S. pombe*, there is an intimate relationship between Plo1 activity and the behaviour of the Dmf1/Mid1 protein, which plays a critical role in establishing the actin ring.

References

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